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Mini Review

Risk factors for endometrial cancer: An umbrella review of the literature

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Although many risk factors could have causal association with endometrial cancer, they are also prone to residual confounding or other biases which could lead to over- or underestimation. This umbrella review evaluates the strength and validity of evidence pertaining risk factors for endometrial cancer. Systematic reviews or meta-analyses of observational studies evaluating the association between non-genetic risk factors and risk of developing or dying from endometrial cancer were identified from inception to April 2018 using PubMed, the Cochrane database and manual reference screening. Evidence was graded strong, highly suggestive, suggestive or weak based on statistical significance of random-effects summary estimate, largest study included, number of cases, between-study heterogeneity, 95% prediction intervals, small study effects, excess significance bias and sensitivity analysis with credibility ceilings. We identified 171 meta-analyses investigating associations between 53 risk factors and endometrial cancer incidence and mortality. Risk factors were categorised: anthropometric indices, dietary intake, physical activity, medical conditions, hormonal therapy use, biochemical markers, gynaecological history and smoking. Of 127 meta-analyses including cohort studies, three associations were graded with strong evidence. Body mass index and waist-to-hip ratio were associated with increased cancer risk in premenopausal women (RR per 5 kg/m^2 1.49; CI 1.39–1.61) and for total endometrial cancer (RR per 0.1unit 1.21; CI 1.13–1.29), respectively. Parity reduced risk of disease (RR 0.66, CI 0.60–0.74). Of many proposed risk factors, only three had strong association without hints of bias. Identification of genuine risk factors associated with endometrial cancer may assist in developing targeted prevention strategies for women at high risk.

Key words: endometrial cancer, gynaecological oncology, uterine cancer, obesity, risk factors, umbrella review
Additional Supporting Information may be found in the online version of this article.
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Introduction

Endometrial cancer is the most common gynaecological cancer and the second most common female malignancy, after breast cancer, in the developed world.[1] In 2012, the number of new cases and deaths due to endometrial cancer worldwide was 319,605 and 76,160 respectively.[1] The age-standardised incidence and mortality rates from endometrial cancer have been rising steadily in most developed countries over the period 1978–2013, which has been attributed mainly to lifestyle factors (e.g., the obesity and diabetes epidemic), increasing age and socioeconomic-driven changes to reproductive factors such as parity.[2] The use of uterine-sparing treatments for dysfunctional menstrual bleeding has also resulted in a reduced number of hysterectomies performed early in life.[3] Endometrial cancer incidence is predicted to continue to rise in the coming decades, in particular among low and middle-income countries.

Several non-genetic risk factors have been associated with an increased risk of endometrial cancer, particularly for the most prevalent histological subtype endometrioid endometrial adenocarcinoma, which include obesity, physical inactivity, excess exogenous oestrogen, insulin resistance,[4] and tamoxifen use after breast cancer,[5–9] whereas daily coffee consumption has been shown to be inversely associated with endometrial cancer.[10–15] Although many of the reported risk factors could have a causal association with endometrial cancer, they could also be over- or underestimated due to residual confounding or other biases, which are common in the epidemiological literature.[16–18] Umbrella reviews can systematically appraise evidence in the published literature by evaluating meta-analyses of multiple putative risk factors on multiple outcomes. Recent umbrella reviews across a broad spectrum of disease outcomes have concluded that only a minority of several published associations have robust data without hints of bias; these included associations between adiposity,[19] diabetes mellitus and cancer incidence and mortality,[20] among others.[21–24]

We performed an umbrella review of systematic reviews and meta-analyses to investigate the strength and validity of the associations between non-genetic risk factors and the risk of developing or dying from endometrial cancer.

Methods

Literature search and eligibility criteria

We searched PubMed and the Cochrane database of systematic reviews from inception to April 2, 2018 for systematic reviews and meta-analyses of observational studies that investigated the association between non-genetic risk factors and risk of endometrial cancer development and death (Supporting Information). We further hand-searched the citations of the retrieved eligible papers to identify additional publications that might have been missed during the initial search and the proceedings of relevant conferences for unpublished data. In this umbrella review the primary analysis focused on cohort studies, representing the best available evidence among observational studies. Sensitivity analyses were conducted including case–control studies.

Inclusion and exclusion criteria

We included systematic reviews with or without meta-analyses of observational epidemiological studies in humans that assessed lifestyle and environmental (non-genetic) risk factors and endometrial cancer incidence or mortality. We excluded studies where endometrial cancer incidence and mortality were not the primary outcomes, studies with benign endometrial pathologies as the primary outcomes of interest (such as fibroids or endometrial polyps), studies exploring the impact of genetic factors as well as studies assessing prognostic risk factors among women diagnosed with endometrial cancer (Supporting Information Figure 1).[25–53] We further excluded narrative reviews and meta-analyses that had only one study, did not report the necessary study-specific data including the relative risk (RR) and 95% confidence intervals (CI) or the number of endometrial cancer cases and controls or total population.[14,54–71] Where two or more meta-analyses examined the exact same association, we chose the largest meta-analysis to avoid duplicate assessment of the same primary studies; the concordance between included and duplicate meta-analyses was explored in a sensitivity analysis (Supporting Information).

Evaluating the strength of evidence by grading criteria

The association of each risk factor with endometrial cancer was graded as strong, highly suggestive, suggestive or weak evidence. To be included in the 'strong evidence' group, the meta-analysis had to present a p-value of the random effects model smaller than 10^{-6}, a threshold that might substantially reduce false positive findings,[72–74] include more than 1000 cancer cases, have an I^2 for heterogeneity less than 50%, the 95% prediction intervals should exclude the null value, and there should be no indication of small study effects or excess significance bias. Similarly, to satisfy the criteria for inclusion into the 'highly suggestive' group, meta-analyses needed a random effects p value smaller than 10^{-6}, include more than 1000 cases, and have a nominally statistically significant largest study (i.e. $p < 0.05$) in the meta-analysis. A 'suggestive' association should meet the after criteria: random effects P smaller than 10^{-3}, and more than 1000 cases. Any remaining meta-analyses where the p-value of the random effects model was nominally statistically significant were considered to present weak evidence. Sensitivity analyses were conducted after further applying the credibility ceiling threshold analysis to account that a single observational study cannot give more than a maximum certainty, c% (credibility ceiling), that the true effect size is in a different direction from the one suggested by the point estimate[75] (Supporting Information).

Evaluation of the quality of included meta-analyses

We assessed the strength and quality of all included meta-analyses using the AMSTAR tool, which uses 11 criterion items to measure the methodological quality of systematic reviews.[76] If the specific criterion is met, one point is allocated. An overall score relating to review quality is then calculated using the sum of the individual scores. A review scoring above 8 is considered high quality, 4 to 7 is a review of moderate quality and below 4 is low quality.

The search algorithms, the data extraction process and the full description of the individual criteria used for grading can be found in the Supporting Information. All statistical analyses were performed using Stata version 13 (College Station, TX) (StatCorp 2013), and all p values were two tailed.

Patient involvement

We did not involve patients in our study. The results will be disseminated to the general public through public presentations and authors' involvement in different charities.

Results

Characteristics of meta-analyses

We identified 61 eligible publications that included 171 meta-analyses of 1354 individual study estimates (Supporting Information Figure 1).[13,77–136] Of these, 604 studies were cohort (45%), whereas 750 (55%) were case–control studies, and one was a pooled analysis of cohort and case–control studies. In all included meta-analyses, there were two to 42 study estimates combined per meta-analysis with a median of five. The median number of cases and total population in each meta-analysis was 3271 and 265,375 respectively. The lowest number of cases in a meta-analysis was 66 and the highest was 37,423, whereas the smallest total population was 709 and highest total population was 6,445,255. In 145 out of the 171 included meta-analyses, there were more than 1000 cases of endometrial cancer.

A total of 53 risk factors were examined in the 171 meta-analyses, which belong to eight broad categories: seven anthropometric indices (i.e. body mass index (BMI), waist to hip ratio (WHR), waist circumference (WC), weight gain (WG), weight, hip circumference and height); 19 dietary factors (e.g. dairy, fish, fruit, isoflavones, meat, nut, vegetable, alcohol, tea, coffee, acrylamide, cholesterol, fat, fatty acids, type of dietary intake, fibre, folate, glycaemic load and glycaemic index); two risk factors including physical activity and sedentary behaviour (recreational, occupational and total sitting time); six risk factors associated with pre-existing medical conditions or interventions (i.e. presence of metabolic syndrome, diabetes mellitus, hypertension, systemic lupus erythematous, polycystic ovarian syndrome and bariatric surgery); nine factors related to medication or hormonal therapy use (i.e. acetaminophen (paracetamol), aspirin, statin, metformin, bisphosphonate, non-steroidal anti-inflammatory drug, ovary stimulating drugs for subfertility, oral contraceptives and intrauterine devices); four biomarkers (i.e. adiponectin, leptin, adiponectin to leptin ratio and insulin/c-peptide level); five risk factors related to past gynaecological history (i.e. age at menarche, age at last birth, breastfeeding, fertility treatment and parity) and smoking.

Of the 171 meta-analyses, we identified 127 meta-analyses that included at least 2 cohort studies assessing 42 risk factors. Two of the 127 meta-analyses reported on endometrial cancer mortality, the remainder on endometrial cancer incidence. These are presented in Supporting Information Tables S1 and S2. Critical appraisal of the evidence in this review focuses on associations from cohort studies, which constitute the best available evidence among observational studies.

Summary effect size

With $p < 0.05$ taken as the threshold of statistical significance, the summary fixed effects estimates were significant in 68 out of the 127 meta-analyses of cohort studies (54%), whereas the summary random effects were significant in 56 meta-analyses (44%) (Supporting Information Table S1). At $p < 0.001$, 54 (43%) and 43 (34%) meta-analyses produced significant summary results using the fixed and random effects model, respectively. At a more stringent threshold of statistical significance ($p < 10^{-6}$), summary fixed effects estimates were significant in 35 (28%) meta-analyses and summary random effects were significant in 22 (17%) meta-analyses. Of the 20 meta-analyses with strongly statistically significant summary random effect estimates, 18 reported an increased risk of endometrial cancer incidence or mortality for the after risk factors: BMI, hip circumference, height, waist circumference, WHR, weight gain, weight, diabetes mellitus and metabolic syndrome. An inverse association with endometrial cancer incidence was suggested for coffee intake and parity (Supporting Information Table S1). The magnitude of the observed summary random effect estimates ranged from a risk ratio of 0.39 to 3.10, with 64% of the estimates falling between 0.80 and 1.20 (Fig. 1).

The association of the largest study included in each meta-analysis was nominally statistically significant in 50 meta-analyses (39%), and the relative risks of the largest studies were more conservative than the summary random effects in 54 (43%) meta-analyses (Supporting Information Table S1).

Heterogeneity between studies

The Q test for heterogeneity was significant at $p \leq 0.10$ in 44 out of 127 meta-analyses (35%). Large heterogeneity (I^2 = 50–75%) was found in 27 (21%) meta-analyses and very large heterogeneity (I^2 > 75%) in 16 (13%) meta-analyses for ten exposures, including alcohol intake, bariatric surgery, diabetes, BMI per 5 kg/m^2, BMI (overweight *vs.* normal), fertility treatment, glycaemic load intake, physical activity, and for Western-style and healthy-style dietary intake pattern (Supporting Information Table S2).

Small study effects

Small study effects (Egger's test p value <0.10 and where more conservative effects in the largest study of a meta-analysis

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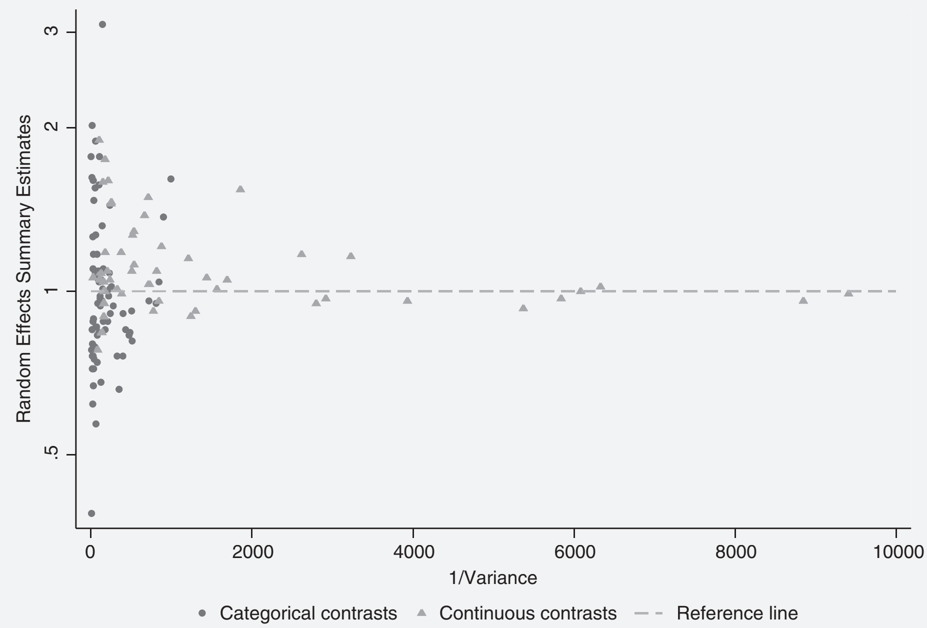

Figure 1. The association between summary random effects estimates and inverse of variance in meta-analyses, stratified by type of exposure-outcome pair.

compared to the summary random effects estimate were recorded) were found to be present in seven meta-analyses for risk factors including age at menarche (per two-year delay in menarcheal age), age at menarche (highest *vs.* lowest), BMI per 5 kg/m^2 (never HRT use, postmenopausal), dietary monounsaturated fatty acid and acrylamide intake, walking time, and coffee intake (heavy *vs.* non-drinker) (Supporting Information Table S2).

Excess significance

Fifteen meta-analyses had evidence of excess significance bias using the largest study estimate as the plausible effect size ($p < 0.10$). These included BMI (in young adulthood, per 5 kg/m^2), weight gain (per 5 kg), weight (per 5 kg), coffee intake (heavy *vs.* non-drinker and per 1 cup/day), monounsaturated fatty acid intake (highest *vs.* lowest), unhealthy and western style dietary intake (highest *vs.* lowest), alcohol intake among postmenopausal women and beer and wine intake (per 10 g/day), aspirin intake, leisure time physical activity (per one hour/week), physical activity (highest *vs.* lowest in women with BMI $\geq$ 25), bisphosphonate use (ever *vs.* never) and age at menarche (per two-year delay in menarcheal age). When either summary fixed, or random effects estimates were alternatively used as plausible effect sizes, excess significance bias was additionally identified for alcohol intake (high *vs.* low drinkers and intake from liquor) (Supporting Information Table S2).

Quality assessment

We assessed the methodological quality of 61 publications that included 171 meta-analyses of observational studies, using the AMSTAR tool (Supporting Information Table S3). The World Cancer Research Fund Continuous Update Project report[116] was not included in this assessment, having already been subjected to extensive peer review processes. Only 12 meta-analyses (20%) provided "*a priori*" published protocols or ethics approval statements. There were at least two independent data extractors and consensus procedures in place where disagreements occurred in only 24 (40%) meta-analyses. Most meta-analyses performed a comprehensive literature search (80%), used appropriate methods to combine the findings (95%), assessed likelihood of publication bias (75%), and provided the characteristics of included studies (98%). Twenty-eight meta-analyses (46%) assessed the scientific quality of included studies and used this assessment to appropriately formulate conclusions (44%). Only two of the included meta-analyses indicated the source of funding for both original studies and meta-analysis. In total, two thirds of the meta-analyses (69%) scored between four to seven points and were considered of moderate quality, nine (15%) scored at least eight points and were considered to be high quality and ten meta-analyses (16%) scored three or less points and were considered low in quality. Low quality meta-analyses as per AMSTAR investigated the following exposures: dietary intake of fruit and vegetables, dietary lipid intake, dietary glycaemic load and index intake, acrylamide intake, aspirin use, intrauterine device use, systemic lupus erythematous, breastfeeding, age at last birth and diabetes.

Grading the evidence

Each of the risk factors identified as being associated with endometrial cancer incidence or mortality was graded into four groups according to the strength of reported evidence in cohort studies: strong, highly suggestive, suggestive or weak evidence (Table 1). Detailed explanation of the assessment criteria is presented in Supporting Information Table S4 (for cohort studies only), while the results for both cohort and case–control studies are shown in Supporting Information Table S5.

Only three out of 127 meta-analyses (2.4%) fulfilled the criteria of strong evidence of an association with endometrial cancer incidence. BMI was associated with an increased risk of endometrial cancer in premenopausal women (RR per 5 kg/m^2 1.49; 95% CI 1.39–1.61). WHR was associated with an increased risk of endometrial cancer overall (RR per 0.1 unit 1.21; 95% CI 1.13–1.29). Parity was associated with reduced risk of endometrial cancer (RR 0.66, 95% CI 0.60–0.74) compared to nulliparous women (Table 1 and Supporting Information Table S4). These three meta-analyses scored five, six and six points on the AMSTAR assessment, respectively, and were hence considered to be of moderate methodological quality.

Thirteen meta-analyses (10.2%) presented highly suggestive evidence and evaluated associations between risk of endometrial cancer and anthropometric indices (n = 10) and diabetes mellitus (n = 3) (Table 1 and Supporting Information Table S4). One meta-analysis graded as highly suggestive, between diabetes and endometrial cancer,[92] scored eight points on AMSTAR assessment, and was considered to be of high methodological quality. The remaining 12 were considered to be of moderate or low quality. Suggestive evidence was found for 14 meta-analyses (11.0%) and weak evidence for 26 meta-analyses (20.5%).

Sensitivity analyses

When both cohort and case–control studies were included in the analysis (Supporting Information Table S5), four additional risk factors presented strong evidence for an inverse association with endometrial cancer incidence: occupational physical activity (highest *versus* lowest category, RR 0.81, 95% CI 0.76–0.87), physical activity (all types, highest *versus* lowest category, RR 0.80, 95% CI 0.74–0.85), smoking (case–control studies only, RR 0.72, 95% CI 0.66–0.79) and smoking among postmenopausal women (RR 0.71, 95% CI 0.65–0.78). These associations provided only suggestive evidence when cohort studies alone were included. The strong association between parity and decreased endometrial cancer risk was downgraded to highly suggestive evidence (RR 0.69, 95% CI 0.65–0.73) when both cohort and case–control studies were evaluated due to the observed high between-study heterogeneity (Supporting Information Table S5).

We found that 44 out of 127 meta-analyses (35%) of cohort studies retained nominal statistical significance ($p < 0.05$) with a credibility ceiling of 0%. With ceilings of 10%, 15% and 20%, 31 (24%), 18 (14%) and 8 (6%) meta-analyses remained statistically significant, respectively (Supporting Information Table S6). All three of the risk factors with strong evidence (BMI per 5 kg/m^2 for premenopausal endometrial cancer, WHR per 0.1 units and parity) remained nominally statistically significant until a 17% credibility ceiling was applied. The 11 risk factors found to have highly suggestive evidence remained nominally statistically significant until a 13% credibility ceiling was applied (Supporting Information Table S6).

We identified more than one published meta-analysis assessing the same risk factors and incidence or mortality of endometrial cancer for 39 of the risk factors identified. For all duplicate meta-analyses (n = 33), there was agreement on the direction, magnitude and statistical significance of the summary associations between the included and excluded meta-analyses (Supporting Information Table S7). When the same evidence grading criteria were applied to these duplicate meta-analyses, the grading was similar in the majority of comparisons. Most of the excluded duplicate meta-analyses also had the same or weaker evidence grading (n = 17 and 16, respectively) compared to included meta-analyses. Of the remaining excluded duplicate studies, coffee intake (n = 2 meta-analyses) and intrauterine device (IUD) use (n = 1) met criteria for a strong association. Glycaemic load intake (n = 1) met suggestive and total fat intake (n = 1) met weak evidence. The cohort studies from the excluded meta-analyses for coffee intake[10–12] were all included in the newer meta-analyses.[13,116] The other excluded meta-analyses also had fewer cohorts included, despite being published more recently.[15,137] Upon further comparison between the two and further investigation of the original studies, the excluded meta-analysis also reported some incorrect relative risks in the analysis. For IUD use, the included meta-analysis was a pooled analysis of 17 studies (four cohort, 13 case–control) from the Epidemiology of Endometrial Cancer Consortium, whereas the smaller excluded meta-analysis included only ten case–control studies. All the studies from the duplicate meta-analysis for glycaemic load intake (eight studies, six cohorts; suggestive evidence) were all found in the larger more recent included meta-analysis (11 studies, seven cohorts; weak evidence). Despite reaching the suggestive evidence category, the older meta-analysis had only one statistically significant study from the eight included.

Discussion

Main findings and interpretation in light of existing evidence

This umbrella review, containing data extracted from 171 meta-analyses of which 127 meta-analyses included at least two cohort studies, suggests that only three meta-analyses presented strong evidence for association with endometrial cancer incidence, reflecting strongly statistically significant results and no suggestion of biases. BMI and WHR were positively associated with endometrial cancer among premenopausal women and overall, respectively, whereas parity was associated with reduced risk of total endometrial cancer. Associations between diabetes mellitus (type one or

Table 1. Summary of evidence grading for meta-analyses of risk factors associated with endometrial cancer incidence or mortality—cohort studies only*

Evidence	Criteria used	Decreased Risk	Increased Risk
Strong	$p < 10^{-6}$‖; >1000 cases; $I^2 < 50\%$; no small study effects¶; prediction interval excludes the null value; no excess significance bias†	***Past gynaecological history***	***Anthropometric indices***
		Parity: parous *vs.* nulliparous	BMI per 5 kg/m^2: premenopausal
			Waist-to-hip ratio: per 0.1 units
Highly Suggestive	$p < 10^{-6}$‖; >1000 cases; $p < 0.05$ of the largest study in a meta-analysis	None	***Anthropometric indices***
			BMI iya: per 5 kg/m^2
			BMI per 5 kg/m^2 increment
			BMI per 5 kg/m^2: Type II
			BMI per 5 kg/m^2: postmenopausal
			BMI per 5 kg/m^2: Type I
			BMI: > 30 *vs.* < 25
			Height: per 10 cm
			Waist circumference: per 10 cm
			Weight gain: per 5 kg
			Weight: per 5 kg
			Pre-existing medical conditions
			Diabetes mellitus (T1/T2): present *vs.* absent (HR)
			Diabetes mellitus (T1/T2): present *vs.* absent (IRR)
			Diabetes mellitus (T1/T2): present *vs.* absent (SIR)
Suggestive	$p < 10^{-3}$‖; >1000 cases	***Dietary intake***	***Physical activity and sedentary behaviour***
		Coffee intake: highest *vs.* lowest category	Sedentary behaviour: highest *vs.* lowest category
		Coffee intake: per 1 cup/day	***Pre-existing medical conditions and interventions***
		Physical activity and sedentary behaviour	Hypertension
		Occupational physical activity: highest *vs.* lowest category	Diabetes mellitus (T1/T2): present *vs.* absent (RR)
		Physical activity: highest *vs.* lowest category	
		Past gynaecological history	
		Age at last birth: per 5-year increment	
		Age at menarche: delay in menarcheal age, per 2-year delay	
		Age at menarche: highest *vs.* lowest category	
		Use of medical/hormonal therapy	
		Metformin use: ever *vs.* never	
		Oral contraceptive: ever *vs.* never use	
		Smoking	
		Smoking: ever *vs.* never**	
		Smoking: ever *vs.* never, postmenopausal	
Weak	$p < 0.05$‖	***Dietary intake***	***Anthropometric indices***
		Animal fat intake: per 10 g/1000 kcal	BMI: per 5 kg/m^2, ever HRT
		Animal-based fat intake: per 30 g increase a day	BMI: per 5 kg/m^2, never HRT
		Carbohydrate intake: per 100 g/day	BMI: > 25 *vs.* < 25
		Decaffeinated coffee intake: per 1 cup/day	BMI: per 5 kg/m^2, mortality

(Continues)

Table 1. Continued

Evidence	Criteria used	Decreased Risk	Increased Risk
		Fibre intake: per 10 g/day	Hip circumference: per 10 cm
		Healthy dietary intake: highest *vs.* lowest category	Weight gain: per 5 kg, ever HRT
		Monounsaturated fatty acid intake: highest *vs.* lowest category	Weight gain: per 5 kg, never HRT
		Total fat intake: per 30 g increase a day	***Dietary intake***
		Physical activity and sedentary behaviour	Glycaemic load intake: highest *vs.* lowest category, obese
		Leisure time physical activity: per 1 h/week	Glycaemic load intake: per 50 units/day
		Pre-existing medical conditions and interventions	Western style pattern dietary intake: highest *vs.* lowest
		Bariatric surgery: yes *vs.* no	***Pre-existing medical conditions***
		Use of medical/hormonal therapy	Diabetes mellitus (T1/T2): present *vs.* absent, mortality
		Bisphosphonate use: ever *vs.* never	Metabolic syndrome: present *vs.* absent
		Past gynaecological history	***Past gynaecological history***
		Breastfeeding: longest *vs.* shortest duration	IVF done: ever *vs.* never
		Smoking	
		Smoking: per 20 cigarettes/day increment**	

Abbreviations: BMI, body mass index; BMI iya, Body mass index in young adulthood; EC, endometrial cancer; ECM, endometrial cancer mortality; HR, hazard ratio; HRT, hormone replacement therapy; IRR, incidence rate ratio; IVF, *in-vitro* fertilisation; RR, relative risk; SIR, standardised incidence ratio; T1 T2, Type 1 or Type 2 diabetes mellitus.
*only meta-analyses meeting at least weak grade of evidence listed.
**only prospective studies were included.
‖p indicates the p values of the meta-analysis random effects model.
¶Small study effect is based on the p value from the Egger's regression asymmetry test ($p > 0.1$) where the random effects summary estimate was larger compared to the point estimate of the largest study in a meta-analysis.
†Based on the p value ($p > 0.1$) of the excess significance test using the largest study (smallest standard error) in a meta-analysis as the plausible effect size.

type two), height and other anthropometric indices (i.e. BMI in young adulthood, waist circumference and weight gain) with endometrial cancer were graded with highly suggestive evidence.

Obesity and endometrial cancer

The majority of meta-analyses (11/17, 64.7%) studying adiposity indices in relation to endometrial cancer incidence and mortality were supported by strong or highly suggestive evidence. Our evidence grading largely agreed with the World Cancer Research Fund Continued Update Project in 2013,[116] where body fatness was deemed to have a 'convincing causal relationship' with endometrial cancer. Similarly, the International Agency for Research on Cancer recently deemed adiposity to be causal for endometrial cancer.[138] Furthermore, our findings are in partial agreement with recent Mendelian Randomisation studies, where genetically elevated BMI, but not WHR, was found to be causally associated with endometrial cancer risk.[139,140] The mechanisms that may underlie the association of obesity with endometrial cancer are not fully characterised but likely include higher oestrogen levels in postmenopausal women, hyperinsulinaemia and a chronic inflammatory state.[4,8,19,141,142] In our review, the evidence for an association between BMI and endometrial cancer was strong for premenopausal cancer, but was highly suggestive for postmenopausal disease due to large between-study heterogeneity, which could be due to a stronger association observed between BMI and endometrial cancer among never-users than among ever-users of HRT (RR 1.90, 95% CI 1.56–2.30, and RR 1.18, 95% CI 1.07–1.31).[78] However, the analyses by HRT use had fewer than 1000 incident cases and were both classified as weak evidence.

Parity and endometrial cancer

We found strong evidence for a 40% reduction in endometrial cancer incidence among parous compared to nulliparous women. A large meta-analysis of 69,681 participants including 10 prospective studies, 35 case–control studies and one pooled analysis suggested a non-linear inverse relationship between parity and endometrial cancer risk.[106] Hormonal changes during pregnancy may explain this association, usually characterised by a shift to greater progesterone production with protective effects on the endometrium. The impact on the timing of endometrial carcinogenesis or for different histological subtypes is less well understood.

Diabetes and endometrial cancer

There was highly suggestive evidence that diabetes mellitus increases the risk of endometrial cancer, although the association with mortality was weak. Our analysis was in line with a previously published umbrella review by Tsilidis and colleagues that reported a summary random effects estimate of 1.97 (1.71–2.27) for endometrial cancer incidence in diabetic patients.[20,143] Hyperinsulinaemia, which is a common phenomenon prior to diabetes onset, likely has a causal association with endometrial cancer,[4,140] either through direct mitogenic effects or possibly by increasing the levels of bioavailable oestrogen through a reduction in sex hormone binding globulin (SHBG) levels.

Additional risk factors for endometrial cancer

There was highly suggestive evidence that adult attained height was associated with increased risk of endometrial cancer. This finding was in partial agreement with the 2013 World Cancer Research Fund Continuous Update Project (WCRF CUP) report judgement as 'limited-suggestive'.[116] More recent data from Aune *et al*. with six additional studies also found height to be significantly associated with endometrial cancer risk (RR 1.15, 95% CI 1.09–1.22).[77] Although it seems biologically improbable that increased height would directly modify endometrial cancer risk, height may act as a marker for genetic and environmental factors affecting women's growth from pre-conception to growth completion.[116] There was suggestive evidence that smoking reduced the risk of endometrial cancer in cohort studies, although the evidence became strong when case–control studies were included.[107] The majority of the published cohort studies showed a reduction in risk of endometrial cancer among current or former smokers compared to never smokers.[144–153] A mechanistic link between an anti-oestrogenic effect of smoking and endometrial cancer risk has been suggested but has limited direct evidence.[154,155] There was suggestive evidence to indicate that physical activity (any type or occupational) was inversely associated with endometrial cancer. This was in agreement with the WCRF report, which found probable causal evidence for an inverse association between physical activity and endometrial cancer.[116] The association between sedentary behaviour and endometrial cancer was supported by suggestive evidence in agreement with the WCRF report.[116] Our findings provided only suggestive evidence that coffee intake decreases the risk of endometrial cancer mainly due to evidence of excess significance bias, which was concordant with the WCRF CUP report and results from another recent review that graded the evidence for an association as probable.[116,156] Two further risk factors, late age at last birth and metformin use, also revealed suggestive evidence for a decrease in endometrial cancer risk. Potential biologically plausible mechanisms for why late age at last birth may protect against endometrial cancer include prolonged progesterone exposure during pregnancy being particularly beneficial in women of older age and the probability of fewer anovulatory cycles in older women who have become pregnant.[124,157] Hypertension, despite adjustment in the meta-analysis for smoking, BMI, oral contraceptive use and parity, was the final risk factor identified within the suggestive evidence category as increasing the risk of endometrial cancer. When both cohort and case–control studies were considered, hypertension had a highly suggestive association with endometrial carcinogenesis. The biological mechanism for this association remains unclear, although it has been suggested that chronic hypertension promotes cellular senescence and inhibition of apoptosis.[158,159]

Strengths and weaknesses

This umbrella review presents the most comprehensive critical appraisal of published associations between risk factors and the risk of developing or dying from endometrial cancer. Categorisation of this evidence was based on a wide range of statistical tests and sensitivity analyses aimed to assess evidence strength and validity. The criteria selected to grade each meta-analysis by evidence level (i.e. strong, highly suggestive, suggestive or weak) is a transparent and systematic way of evaluating the strength of evidence in the literature.

Nevertheless, possible limitations and caveats should be considered. This review relies on literature searches conducted by the original authors and the results of already published systematic reviews and meta-analyses. Although it is possible that some studies were missed in the original searches, it is unlikely that this has impacted our results, as the assessment of duplicate meta-analyses led to similar results. The statistical tests we used to explore presence of bias can only offer hints of bias, but do not prove its definitive presence or its exact source. However, our estimates are likely to be conservative, as a negative test for bias does not exclude the potential for it being present. Furthermore, the number of studies showing separate results by pre- and post-menopausal women was low. Analyses stratified by menopausal status could therefore not be conducted other than for BMI, weight gain and smoking, which may miss important exposures for a cancer type that is hormonally driven and is most commonly diagnosed in postmenopausal women. The single meta-analysis identified on association of postmenopausal hormone replacement therapy use and endometrial cancer incidence was excluded from this umbrella due to a lack of study-specific data.[160] Conducting sensitivity analyses according to the histological subtype of endometrial cancer was not possible, as this data was not provided in the individual studies, but is likely to be highly relevant.

Conclusions

This umbrella review provides a comprehensive summary of the body of published systematic reviews and meta-analyses examining risk factors and the incidence and mortality from endometrial cancer. There is a strong association between BMI (per 5 kg/m^2) and waist-to-hip ratio (per 0.1 unit) and an increased risk of pre-menopausal and total endometrial cancer, respectively. A reduced risk of endometrial cancer in parous *versus* nulliparous women is also strongly associated. Although there are other exposures which may be associated with an increased or decreased risk of this cancer, their association is less certain and firm conclusions cannot be drawn at this time.

The identification of risk factors that are robustly associated with risk of endometrial cancer can help the identification of high-risk groups of women that would benefit from targeted prevention strategies. Our findings emphasise that obesity is a major risk factor for endometrial cancer and highlights the importance of weight control programs in mitigating the further rise in incidence of this malignancy. Hormonal and metabolic pathways that underlie the association of adiposity with endometrial cancer, as well as for diabetes and parity, require further characterisation as they may offer potential targets for preventive strategies in higher risk women.

Authors' contributions

The study was conceived and designed by MK, EP, PMH and KT. The data was acquired and collated by OR, IK, MK, SC and analysed by OR, IK, MK, GM, SC and KT. The study was drafted and revised critically for important intellectual content by all authors (OR, IK, GM, SC, MG, JN, HG, EP, PMH, KT, MK). All authors gave final approval of the version to be published and have contributed to the study. Article guarantor: Dr Maria Kyrgiou. No ethical approval required.

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no relationships or activities that could appear to have influenced the submitted work.

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